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Conclusiveness of rechallenge in the interpretation of adverse drug reactions

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1 We here consider the extent to which the presumed correlation between an adverse event and the administration of a particular drug can be reinforced by rechallenge. A first question of terminology is: what is a rechallenge?
2 Rechallenge is often accepted too readily as proof of a causal relationship and clinical examples give illustrations of common misinterpretations.
3 Definitions are proposed to characterize: (i) the outcome of rechallenge; (ii) the conditions under which rechallenge is performed.
4 In discussing causality, a sharp distinction is drawn between the outcome *per se* and the establishment of a causal relationship.
5 Finally, the simple concepts proposed here should permit to establish a typology of rechallenge and to assess, by further experimental or retrospective research, the conclusiveness of rechallenge in interpreting adverse drug reactions.

Keywords adverse drug reactions assessment rechallenge

Introduction

Rechallenge is defined as the readministration of a drug suspected to be a possible cause of an adverse reaction, and which has been subsequently discontinued (Stephens, 1983). Although this is not a common procedure, it is sometimes the pivotal event leading to a report or publication of a new adverse effect. Despite the overwhelming importance of rechallenge in the majority of current methods for assessment of adverse drug reactions (ADRs) (Loupi *et al.*, 1984) there has been very little methodological work concerning rechallenge (Stephens, 1983, 1985). An attempt is made here to clarify some of the major issues in the conduct and interpretation of drug rechallenge.

What is a rechallenge?

The definition of rechallenge is itself rather ambiguous; some authors consider that, following a reduction in dosage, a substantial increase in dosage constitutes a rechallenge (Kramer *et al.*, 1979) and that any exacerbation of adverse reactions under such circumstances is clearly suggestive of a drug-induced phenomenon. So as to eliminate any possible ambiguity, in the present discussion the definition of rechallenge has been limited to readministration of a drug that had previously been completely withdrawn for a certain time period. The importance of precision concerning duration of interruption is illustrated by the following example.

Case no. 1 During treatment with drug A (one tablet daily) this patient reported headache beginning within 15 min of drug administration, and lasting for approximately 2 h.

In this case, is each administration to be considered as a rechallenge? This must clearly be defined in terms of the d/e ratio, where d is the total duration of the side-effect and e the time between two successive doses. Here again, we consider that certain limits are necessary in order

to provide an acceptable degree of precision; the following definition is proposed:

Definition 1
Rechallenge is the readministration of a drug which was previously administered and then discontinued. The duration of discontinuation must be sufficient for complete drug elimination. When an adverse reaction appears during the first treatment period, the interruption must also be longer than the time to complete resolution of the reaction (clinical and laboratory).

A drug may accumulate in a target organ and thus it may be difficult to determine if drug elimination is complete. Another complication is that the side effect may be caused by a metabolite. From an operational standpoint, however, in order to eliminate gross ambiguities like those reported before, let us suggest that the duration of discontinuation should be more than five times the half-life of elimination (i.e. the time generally considered as necessary for drug elimination from plasma).

What is a positive rechallenge?

Clinical examples

Case no. 2 This female patient had been taking practolol for 12 months (300 mg day^{-1}) when she developed an eczematous eruption; the rash cleared following treatment with a topical corticosteroid without withdrawal of practolol. One month after the end of topical treatment, the rash recurred, and within 4 months the patient had developed a widespread psoriasiform rash. Practolol was stopped and local corticosteroids were again administered. The skin returned completely to normal within less than 6 weeks. The patient subsequently agreed to oral rechallenge with practolol; she was told to take one tablet (100 mg) every 12 h. Five days later she noted pruritus, followed by development of an erythematous macular eruption. One month later, she was rechallenged and developed pruritus with widespread erythematous macular rash 4 h after a single tablet of practolol (Felix *et al.*, 1974).

Case no. 3 Immediately after the first dose of a newly-marketed drug, a female patient complained of nausea and severe stomach ache; she decided to stop treatment. One week later the drug was readministered upon medical advice; immediately after the first dose, the patient redeveloped the same symptoms with the same degree of severity.

Case no. 4 A 6-month old boy was treated with antimicrobial agent for an episode of fever and diarrhoea. On the second day of treatment, he developed a cutaneous rash lasting for 3 days. Six months later, the same drug was readministered for similar gastro-intestinal disorders; as before, the same type of transient rash developed.

Case no. 5 One week after the beginning of treatment with drug B, there was onset of pruritus with widespread erythematous eruption. Treatment was stopped and there was complete resolution within 4 days. Two weeks later, the patient was rechallenged with the same dose; within 2 days there was development of severe pruritus of the hands and forearms, and drug B was withdrawn.

Each of these four cases was initially reported as an example of 'positive rechallenge' and the physicians rated the correlation between drug administration and the reaction as probable or definite. Nevertheless, the clinical pattern is not self-evident, and requires further analysis.

In case no. 2 there were objective and relatively similar signs during each rechallenge. The decrease in latency to development of the adverse reaction was particularly striking, suggesting that each readministration led to an allergic-like facilitation. Under such circumstances, it can be reasonably assumed that a drug hazard has been well established.

The next case (no. 3) is quite different since there were no objective signs, and the gastrointestinal disorders were reported by the patient herself. The lack of specificity of the gastrointestinal syndrome renders causal assessment more difficult and various psychological factors could clearly be involved. Thus, along with questions arising from the intrinsic subjectivity of certain adverse reactions, there is a problem of causality: would the same symptoms have recurred in the event of a blind rechallenge with placebo?

Case no. 4 illustrates another common type of bias, the protopathic bias (Stephens, 1985); although signs are clearly objective, rash is not uncommon in pediatric gastrointestinal syndromes and it is thus difficult to differentiate between the two possible aetiologies (Figure 1).

The possibility that the rash was not correlated with the drug cannot be ruled out here, and in this case, I do not think that a positive rechallenge would be an important factor for the assessment of causality; aetiological diagnosis must be based on other factors such as the type of rash, the differential diagnosis, the pharmacologic profile of the drug, laboratory tests, etc.

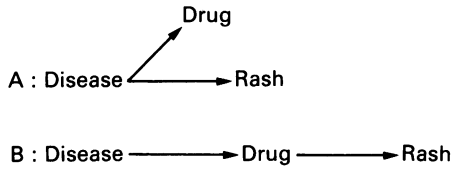

Figure 1 Protopathic bias. A: Rash is a sign of the disease. B: Rash is induced by the corrective treatment of the disease.

Case no. 5 presents another problem: inadequate analysis of clinical events. Rechallenge was considered positive despite the shift from objective signs to subjective symptoms; the physician did not observe the recurrence of rash but simply noted a report of pruritus. In contrast with case no. 2 where there was a clear aggravation, only minimal symptomatology was seen: well-delimited pruritus *vs* a widespread rash. While it can be argued that it was ethically unacceptable to continue rechallenge, in view of the risk of development of a severe, generalized rash, results of this limited rechallenge must be considered as inconclusive.

Definitions

The above discussion points to the importance of establishing a sharp distinction between the objective or factual *results* of rechallenge and its interpretation in terms of causality. Results could be defined as follows:

Definition 2

(i) *Rechallenge will be said to be positive (P) if there is recurrence of the same signs or symptoms as those which previously entailed discontinuation of treatment. The outcome will be type-1 positive (P1) when the same reaction is seen with lesser severity, type-2 positive (P2) when the same reaction occurs with a similar degree of severity, and type-3 positive (P3) when the same reaction is seen but with increased severity.*

(ii) *Rechallenge will be said to be suggestive (S) when the observed reaction, while not identical to that seen initially, could constitute a prodrome of the reaction initially requiring withdrawal of treatment.*

(iii) *Rechallenge will be said to be negative (N) when it is neither positive nor suggestive.*

Of primary importance here is the fact that causality cannot be considered to be relevant at this stage. It is thus perfectly legitimate to take both symptoms and signs into account for evaluation of the outcome of rechallenge; however, it is essential to specify whether the positive result was for signs, symptoms or both. In case no. 2, the outcome is obviously P3 for rash; since in some cases pruritus may be considered to be a prodrome for skin rash (see cases 19 and 21 in **Appendix**) in case no. 5 the outcome of rechallenge could be rated P1 for pruritus and S for rash.

The following decision table (Table 1) is an operational tool for evaluation of the outcome of rechallenge:

Table 1 Decision table for evaluation of the outcome of rechallenge

Identical reaction	Y	Y	Y	N	N
Increased Sev. or Loc. or decreased time lag	Y	N	N	—	—
Unchanged Sev., Loc. and Time lag	—	Y	N	—	—
Possible prodrome	—	—	—	Y	N
Outcome of rechallenge	P3	P2	P1	S	N

Sev. = Severity of adverse effect
Loc. = Localization
Time lag = Time between the first dose and the onset of the adverse effect
Y = Yes
N = No
— = Irrelevant

The definition of increased severity for a given symptom should be self-evident (e.g. greater increase in SGOT, more severe itch, etc.). A skin rash may be more widespread after rechallenge, and this is a good example of what is meant by an extended localization; this is also the case for hepatic side-effects with impairment of more hepatic functions after rechallenge, or blood dyscrasias extending to additional blood cell lines.

Conditions of rechallenge

Before considering the issue of causality, it is necessary to define conditions under which rechallenge is performed. An additional definition is thus suggested:

Definition 3

The conditions under which rechallenge is performed will be said to be:

- *Minimal (m) when the rechallenge dosage is less than the dosage of the previous treatment;*

- *Constant (C) when the dosage is the same during rechallenge as during the previous treatment;*
- *Maximal (M) when the rechallenge dosage in any way exceeds that of the previous treatment.*

Type M conditions can occur in cases of unintentional rechallenge, when the first break in treatment is fortuitous and a causal relationship between the drug and the reaction is not yet suspected.

A second decision table (Table 2) is proposed for rechallenge conditions:

Table 2 Decision table for rechallenge conditions

S.D. or D.D. increased or I.D. shortened	Y	N	N
S.D., D.D. and I.D. unchanged	–	Y	N
Rechallenge conditions	M	C	m

S.D. = Single dose
D.D. = Daily dose
I.D. = Interval between two successive doses

Conclusive value of rechallenge

In view of the above, each rechallenge is characterized by two *neutral* parameters: one concerning conditions under which rechallenge is performed, and the other qualifying the outcome. By 'neutral' it is meant that assigning a value to these parameters is as non-interpretative ('objective') as possible. Case no. 2 (practolol) could be considered m/P3; case no. 4 (antimicrobial agent) C/P2. How will this be interpreted in terms of causality?

Subjective complaints (Reidenberg & Lowenthal, 1968; Schindel, 1974)

Nausea, headache, and asthenia are subjective symptoms; nevertheless, amongst subjective complaints we can class events such as vomiting which could be observed by a person other than the patient, but where psychological induction cannot be ruled out, i.e. when the objective change could be produced by placebo. The generalized acceptance of double-blind methodology partly results from this risk of psychological induction. Although a blind rechallenge against placebo could be of value when an objective adverse reaction can be shown (Stephens, 1983), under the usual conditions of clinical practice administration of such a placebo is very difficult. On the other hand, it is suggested that when a complaint is purely subjective, rechallenge is quite useless or even misleading. While the possibility that a drug could induce digestive symptoms or asthenia cannot, of course, be excluded, I do not consider that rechallenge would be useful for the establishment of causality in this case.

Objective signs

For certain adverse reactions (laboratory abnormalities, hepatitis, etc.) psychological induction is considered highly unlikely, and in such cases, the question of the conclusive value of rechallenge must be posed. 'Conclusive value' is not a measure of causality, and simply corresponds to the degree to which results of rechallenge further implicate the drug as a causal factor for the adverse effect. If conclusive value were rated nil, this would not mean that a causal role of the drug can be excluded or considered unlikely; it would simply indicate that the rechallenge provides no *additional* information, without prejudice to other criteria for causal assessment (timing, symptomatology, laboratory tests, etc.).

I have suggested elsewhere that certain retrospective studies could provide epidemiological data for development of more objective methods for the assessment of ADRs (Girard, 1984); one example is shown in Table 3. A literature review concerning cutaneous rash following treatment with practolol yielded a total of 24 case reports for which sufficient information was available (Felix *et al.*, 1974; Kauppinen *et al.*, 1976; Row-

Table 3 An example of retrospective studies providing data for development of more objective methods for the assessment of ADRs

	Condition			
Outcome	m	C	M	Total
N	–	–	–	
S	1 (0.07)*	1 (0.14)		2
PI	–	–	–	
P2	–	–	–	
P3	15 (0.93)	6 (0.86)	1 (1)	22
Total	16	7	1	24

*In parentheses the relative cell frequency, i.e. the quotient of the absolute number over the total for the corresponding column.

land & Stevenson, 1972; Sondergaard *et al.*, 1976). In six cases it was necessary to assume that the daily oral rechallenge dose was 200 mg (two 100 mg tablets); the exact dosage (200 mg daily) is known in the remaining 18 cases (see **Appendix**). Despite the small population size, the distribution of these 24 cases in Table 3 is highly suggestive of a drug reaction, and in this case the conclusive value of rechallenge seems very high.

Retrospective studies concerning a few types of drugs and a limited number of adverse reactions could provide useful information and could help to define the power and limits of the rechallenge criterion for the assessment of ADRs. As is clear from the practolol example, the published literature is not necessarily a good source of adequately documented reports, and retrospective studies could allow analysis of more complete data supplied by the manufacturer or by regulatory agencies, without instituting an excessively adversarial climate.

It is important to stress that the present paper does not claim to solve the difficult question of causality, but aims to formulate it as clearly as possible. Two parameters which are simple, unambiguous and easy to use, were proposed in order to characterize each rechallenge. The aim is only to develop a conceptual and terminological framework to facilitate further experimental work on the causal assessment of ADRs; this work requires a detailed, multifactorial analysis.

As in the case of practolol previously studied, the conclusive value of rechallenge will be high when: (i) for some reason or other (timing, dechallenge, etc.), the probability of a drug causal relationship is high; (ii) and rechallenges, when performed, are positive in most cases. It is also possible to examine if for a certain side-effect and a certain drug, the rechallenges have the same outcome in patients with the same characteristics (age, sex, dosage, etc.). Finally, one could distinguish between ADRs where rechallenge is, say, m/P3 and those where it is C/N or C/S: from a prospective standpoint, it would become possible to discriminate the drug-induced diseases where rechallenge has a value in aetiological diagnosis and those where it is probably of little use.

Fallacious rechallenge

Before closing our discussion of causality, it would be useful to consider one other common situation. When an adverse reaction develops in a patient taking two different drugs (A and B) the physician may choose to withdraw both. If for some reason a cautious rechallenge is made with drug B (for example, further treatment is viewed as absolutely necessary for the patient) and the adverse reaction does not recur, the physician concludes or suggests that the adverse reaction was probably a side-effect of drug A. This is clearly false: a negative rechallenge with drug B is in no way equivalent to a positive rechallenge with drug A!

Data quality

The previous examples have illustrated the risk of misleading or false analysis due to inadequately documented reports; this makes it indispensable that a high standard of quality be maintained in reporting adverse effects. I will not here seek to extend quality criteria which have been presented elsewhere (Girard, 1986b), but will simply list several which appear crucial for sound interpretation of the results of rechallenge:

—Maintaining a sharp distinction between description and interpretation—broad statements such as 'positive rechallenge' should be avoided;
—Discrimination between objective signs and subjective symptoms;
—Careful reporting of the dosage and timing of the various treatments, withdrawals, rechallenge, etc.;
—Careful exploration of the various possible aetiologies of the reaction; the emphasis which I have given to possible psychological factors in some side-effects is relevant to this problem of differential diagnosis.

Ethics

The present paper must not be considered to be an invitation to carry out rechallenge; there are some major ethical problems. Nevertheless, besides those cases where the physician makes the decision to carry out rechallenge with the informed consent of the patient, there are other situations where rechallenge may be seen:

—When the suspected drug is vital to the patient;
—When rechallenge is fortuitous, the drug in question not being suspected before the second administration.

As is often the case in science, scattered data may give precious information provided that they can be analyzed in an accurate and timely fashion. Methodology must be refined so as to allow extraction of the greatest possible quantity of information from these potentially significant but rather scarce reports.

Discussion and conclusions

Since appropriate evaluation of rechallenge requires input from clinical pharmacology and fundamental research, numerous questions could be raised, e.g.:

—In the case of allergic phenomena, should rechallenge be expected to cause a more severe reaction? Under constant conditions, should the outcome be P3?

—On the other hand, is it possible that under certain circumstances a false-negative will be seen, as if the patient had developed a period of 'desensitisation' following the first occurrence of the side-effect?

—Can a causal relationship be excluded on the basis of negative outcome of a rechallenge?

—How should the outcome of rechallenge be interpreted when a phenomenon is seen to be unrelated to that occurring in the previous administration (e.g. conjunctivitis first, peritonitis during rechallenge)?

Although retrospective studies are not usually a major component of drug surveillance programmes, they can make an important contribution to the assessment of drug reactions, provided that rigorous rules are used for quality control of data.

Part of the difficulties in interpreting rechallenge are in connection with the ambiguity of the word; moreover, data concerning rechallenge are qualitative and thus difficult to manage and analyze. However the requirement for reliable methodology does not preclude the use of 'soft data' (Feinstein, 1970), as long as these data can be defined in a fashion sufficiently precise so that they have the same meaning for everyone who uses them (Wasson *et al.*, 1985). The use of two straightforward parameters (condition; outcome), which are aimed to characterize each rechallenge, should facilitate the acquisition and coding of data and their analysis in a great number of cases.

The simple concepts proposed in this paper should permit to establish a typology of rechallenge: in conditions A and B with adverse reaction C and D, what were the outcomes of rechallenges when they were performed? More generally, I think that typologies like this one could be established for other criteria which are often considered as relevant for the causal assessment of ADRs or for the discovery of high-risk groups of patients; these criteria are, for example, timings, dosages, associated treatments or diseases, age, sex, etc.

Such work of classification could be a first step towards a genuine semiology (i.e. a precise description of signs and symptoms) of drug-induced diseases, which, in itself, would be a major achievement in clinical pharmacology (Girard, 1986a).

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Appendix

(Published cases of rechallenge on practolol (for which information required by Table 3 is available).)

Patients	*Age (years)*	*Sex*	*Dose of practolol (mg day^{-1})*	*Duration of treatment before onset of the rash (months)*	*Dose of practolol during rechallenge (mg day^{-1})*	*Time of onset of the first symptoms after rechallenge*	*Conditions of rechallenge*	*Outcome of rechallenge*
1 (Felix *et al.*, 1974)	61	F	300	4	200	36 h	m	P3
2 (Felix *et al.*, 1974)	60	M	300	15	200	36 h	m	P3
3 (Felix *et al.*, 1974)	54	F	400	1	200	36 h	m	P3
4 (Felix *et al.*, 1974)	61	F	100	18	200	36 h	M	P3
5 (Felix *et al.*, 1974)	59	F	300	18	200	4 weeks	m	P3
6 (Felix *et al.*, 1974)	55	F	300	3 weeks	200	36 h	m	P3
7 (Felix *et al.*, 1974)	45	F	300	12	200	5 days	m	P3
8 (Felix *et al.*, 1974)	66	F	300	18	200	36 h	m	P3
9 (Felix *et al.*, 1974)	56	M	300	9	200	36 h	m	P3
10 (Felix *et al.*, 1974)	60	F	300	11	200	36 h	m	P3
11 (Felix *et al.*, 1974)	78	M	300	1	200	4 days	m	P3
12 (Felix, *et al.*, 1974)	63	M	200–300	20	200	36 h	C	P3
13 (Kauppinen *et al.*, 1976)	48	F	200	4	200	3 days	C	P3
14 (Kauppinen *et al.*, 1976)	75	F	200	5	200	9 days	C	P3
15 (Kauppinen *et al.*, 1976)	51	M	300	18	200	9 days	m	P3
16 (Kauppinen *et al.*, 1976)	69	M	300	30	200	7 days	m	P3
17 (Kauppinen *et al.*, 1976)	75	M	200	72	200	10 days	C	P3
18 (Kauppinen *et al.*, 1976)	69	F	200	24	200	10 days	C	P3
19 (Rowland & Stevenson, 1972)	75	F	200	1	–	5 days	C	S
20 (Sondergaard *et al.*, 1976)	65	F	300	16	–	⩽ 3 days	m	P3
21 (Sondergaard *et al.*, 1976)	55	M	300	26	–	⩽ 3 days	m	S
22 (Sondergaard *et al.*, 1976)	45	M	300	1	–	1 week	m	P3
23 (Sondergaard *et al.*, 1976)	68	M	300	24	–	1 week	m	P3
24 (Sondergaard *et al.*, 1976)	43	F	200	16	–	⩽ 3 days	C	P3

The daily dose for rechallenge was not available for the last six patients (nos 19, 20, 21, 22, 23, 24); it is assumed to be 200 mg, as in the remaining 18 cases.

Results for patient 19 are not clear: severe pruritus and widespread exfoliative rash developed with practolol. Within 5 days of rechallenge, severe generalized pruritus recurred, and the patient reported feeling ill; the drug was withdrawn, and pruritus resolved within four days. The primary criterion in Table 3 is the recurrence of rash with practolol rechallenge, and pruritus is here considered to be a possible prodrome to rash; this also holds true for case no. 21. Furthermore, the report indicates that of three patients (nos 21, 22 and 23) rash developed in two, while a third complained of pruritus; for the sake of simplicity, this patient is here identified as case no 21; however this arbitrary choice is without effect on Table 3, which shows frequency only.